Hypercalcemia

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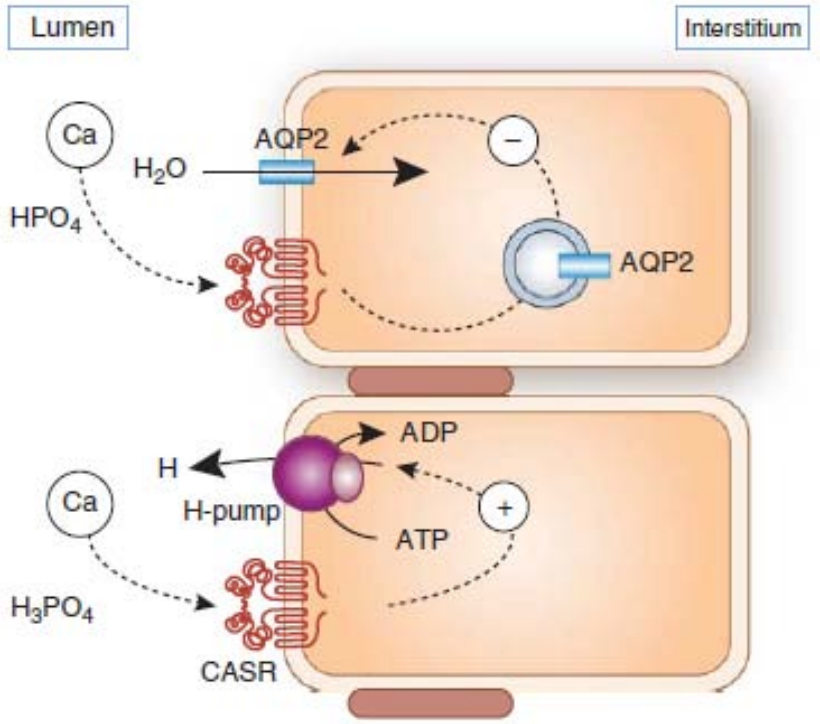
Clinical Manifestations

- Severity of symptoms depends on the degree and rate of rise in serum calcium
- Gastrointestinal symptoms
  - Nausea, vomiting, constipation, abdominal pain, and rarely, PUD or pancreatitis
- Neuromuscular involvement
  - Altered mentation, impaired concentration, fatigue, lethargy, muscle weakness
- Cardiovascular effects
  - HTN
  - Shortening of the QT interval on the EKG
  - Amplification of digitalis toxicity
- Ocular symptoms
  - Conjunctivitis from crystal deposition
  - Rarely, band keratopathy (deposition of calcium in band like pattern across the cornea

Renal Effects

- Defect in urinary concentrating ability (nephrogenic diabetes insipidous)
- Volume depletion from resulting diuresis
- Nephrolithiasis
- Nephrocalcinosis
- Decrease in GFR from direct renal vasoconstriction and volume depletion

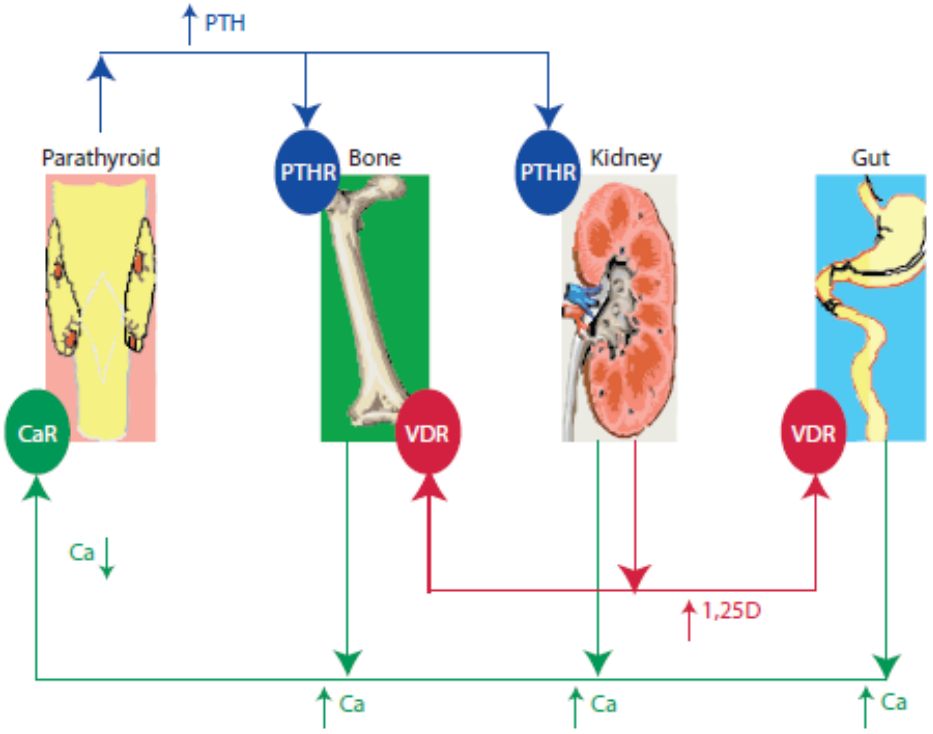


- When the [Ca+] in the tubular fluid increases, two counterbalancing mechanisms are activated by the CASR in the distal tubule:
  - CASR stimulates proton excretion by the H-pump in the intercalated cells
  - Decreases water reabsorption by reducing aquaporin 2 (AQP2) expression on the apical membrane
  - Urine dilution and acidification protect against calcium-phosphate salt precipitation within the tubular lumen

Vezzoli, et al. KI 2011; 80: 587-593

Etiologies

- Malignancy
- Hyperparathyroidism
- Thyrotoxicosis
- Granulomatous diseases
- Familial hypocalciuric hypercalcemia
- Drug-induced
  - Vitamin D
  - Thiazide diuretics
  - Estrogens and anitestrogens
  - Androgens (breast ca therapy)
  - Vitamin A
  - Lithium
- Immobilization
- Total parenteral nutrition



Peacock. CJASN 2010; 5: S23-S30

Pathophysiology in Malignancy

- Osteolytic Metastases – induction of local osteolysis by tumor cells
  - Approximately 20% of cases of hypercalcemia in malignancy
  - Common in solid tumors and multiple myeloma, less common in leukemia and lymphoma; Breast cancer is most common
  - Release of osteoclast activating factors by tumor cells: Il-6 and locally-produced PTH-rp, which increases expression of receptor activator of nuclear factor kappa B ligand (RANKL) in bone
  - RANKL binds to RANK on surface of osteoclasts precursors, stimulates differentiation
- Humoral hypercalemia of malignancy (HHM)
  - Most common cause of hypercalcemia in malignancy (up to 80%)
  - Secretion of PTH-rP
  - Some homology with PTH, especially at the amino-terminal end, allows it to bind to PTH-1 receptor and stimulate bone resorption and distal tubular calcium reabsorption
  - Less likely than PTH to stimulate 1-25 dihydroxyvitamin D production
  - Results in suppression of endogenous PTH

Pathophysiology, cont'd

- Increased production of 1,25-Dihydroxyvitamin D
  - The cause in almost all cases in Hodgkin lymphoma and approximately 1/3 of cases in NHL
  - Usually conversion of 25-hydroxyvitamin D -> 1-25-dihydroxyvitiman D controlled by PTH and [serum phosphate]
  - Lack of suppression of 1-25- D production by PTH-independent extrarenal production of 1-25 D from 25-OH Vit D by malignant lymphocytes

Treatment

- Saline hydration
  - Restoration of intravascular volume, increases urinary calcium excretion
- Loop diuretics
  - Increased urinary excretion
- Calcitonin
  - Increases renal Ca++ excretion and interferes with osteoclast maturation
  - Works rapidly, lowering serum Ca by maximun 1-2 mg/dl within 4-6 hours
  - Of limited use because tachyphylaxis develops
- Bisphosphonates
  - Onset within 24-72 hrs; more sustained effect

Treatment, continued

- Glucocorticoids (onset in 2-5 days)
  - Decrease intestinal calcium absorption
  - Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in pts with granulomatous diseases or lymphoma
- Gallium nitrate or Ganite (onset in 3-5 days)
  - Inhibits osteoclast-mediated bone resorption
- Dialysis
  - Low or no calcium dialysate

Bisphosphonates: Mechanism of Action

- In the extracellular space:
  - Act as calcium chelators, binding to and stablizing calcium phosphate within the bone matrix and preventing dissolution
- Intracellular effects (within osteoclasts):
  - Inhibition of the mevalonate pathway, which is responsible for post-translational lipid modification and anchoring of small GTPases in cell membranes
  - Interrupts a variety of cell processes, including integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis
  - Through incorporation into ATP analogues, can also impair cell energetics via inhibition of ATP-dependent metabolic pathways
  - Disrupt the osteoclast cytoskeleton by inhibiting actin assembly

Bisphosphonates: Pharmacokinetics

- Distributed between bone and extracellular fluid
- Remain in bone for months to years; once incorporated into bone, remain inactive until they are released by osteoclast activity
- Within the serum, variable protein binding
  - Ibandronate 87%, Zolendronate 56%, Pamidronate 54%
- IV forms are not metabolized, but excreted unchanged by the kidneys by glomerular filtration, with some component of tubular secretion as renal clearance of bisphosphonates exceeds GFR
- As a result, impaired renal function can lead to excessive serum and bone levels with resultant toxicity

Pamidronate vs. Zolendronic acid

- Two identical, concurrent, parallel, multicenter, randomized double-blind, double-dummy trials conducted to investigate the clinical efficacy of ZA (4mg and 8mg) vs . Pamidronate 90mg in the treatment of moderate-severe HCM
- 287 patients: > 18 yrs, histological or cytological confirmed cancer, and severe hypercalcemia with CSC > 3.00 mmol/l (12.0 mg/dl)
- Included patients with renal failure, but excluded patients with Cr > 4.5 mg/dl
- Patients were randomized to receive either 5min of ZA (4mg vs 8mg) vs 2 hr of Pamidronate (90mg); all pts also got saline infusions
- Followed for 56 days or until relapse (CSC > 2.90 mmol/L or 11.6 mg/dL)
- Refractory pts were re-treated with ZA 8mg IV

Major, et al. J of Clin Onc. 2001; 19: 558-567

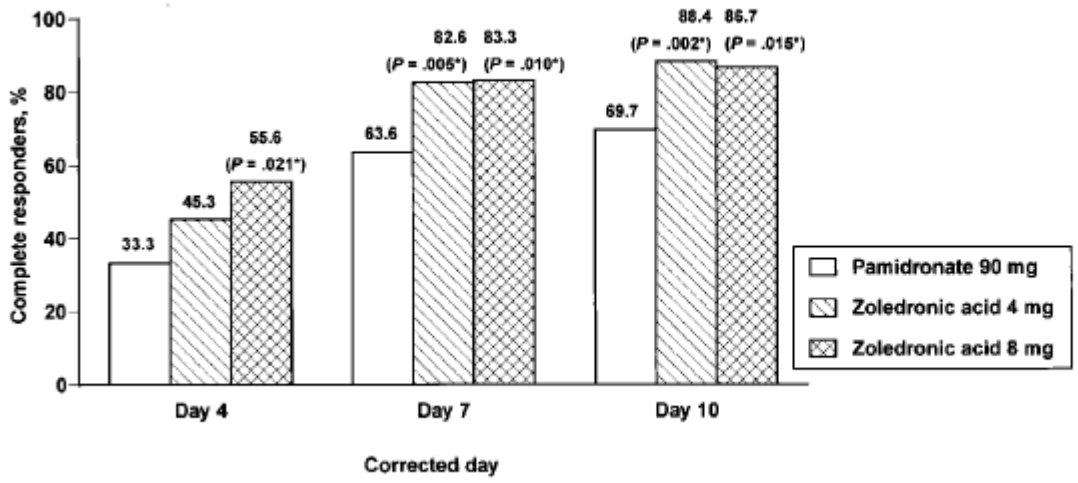


Fig 2. Percent of patients achieving a CR (CSC ≤ 2.7 mmol/L [10.8 mg/dL]). *Statistical significance versus pamidronate. Corrected day: day 4 = days 2-5; day 7 = days 6-8, day 10 = days 9-11.

- Significant difference in % of patients achieving CR (defined as normalization of Ca++ to < 10.8mg/dL by day 10) between ZA and Pamidronate
- No significant differences between the two doses of ZA

Major, et al. J of Clin Onc. 2001; 19: 558-567

Table 4. Number of Patients With Common Toxicity Criteria Grade 3 or 4 Serum Creatinine Values

	Zoledronic Acid 4 mg (n = 86)		Zoledronic Acid 8 mg (n = 96)		Pamidronate 90 mg (n = 100)		Re-Treatment Zoledronic Acid 8 mg (n = 68)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Serum creatinine								
Grade 3	2	2.3	3	3.1	3	3.0	1	1.5
Grade 4		0	2	2.1	1	1.0	1	1.5

- Two patients in the ZA 8mg group and one patient in the Pamidronate 90mg group developed “grade 4” serum Cr levels
- Two patients in the ZA 4mg group and 3 pts in each the ZA 8mg group and the Pamidronate group developed “grade 3”

Major, et al. J of Clin Onc. 2001; 19: 558-567

Bisphosphonate Nephrotoxicity

Pamidronate and Collapsing FSGS

- Case series of 7 patients who were older, Caucasian, HIV negative, who developed collapsing FSGS during active treatment of malignancy
  - Multiple myeloma in 6 pts, breast cancer in 1
- Chemotherapy agents included:
  - Vincristrine in 4
  - Doxorubicin in 5
  - Cisplatin in 2
- Only agent common to all 7 pts was Pamidronate

Markowitz, et al. JASN 2001; 12: 1164-1172

- They all began tx with Pamidronate at or below the recommended dose of 90mg IV monthly, but it was increased to 180mg IV in 2 pts and 360mg IV in 3 pts
- 15-48 mos of treatment before renal insufficiency occurred
- Mean serum creatinine 3.6 mg/dl
- Nephrotic syndrome with mean 24-hr urinary protein excretion of 12.4 g/d

Table 2. Pathologic findings for patients with pamidronate-associated FSGS[a]

Finding	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Total no. of glomeruli	6	35	17	28	4	14	16
no. with FSGS	2	4	5	4	3	4	2
no. with global GS	2	3	8	3	0	1	8
FSGS pattern	Collapsing	Collapsing	Collapsing	Collapsing	Collapsing	Collapsing	Collapsing
Tubular injury	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse
TA and IF	Severe	Moderate	Moderate	Mild	Moderate	Mild	Mild
PCD-associated disease	No	No	No	No	No	No	No
Immunofluorescence	Negative	Negative	Negative	Segmental IgM/C3	Negative	Negative	Segmental IgM/C3
EM, deposits	No	No	No	No	No	NA	No
EM, foot process fusion (%)	95	100	90	60	100	NA	60

[a] GS, glomerulosclerosis; TA and IF, tubular atrophy and interstitial fibrosis; PCD, plasma cell dyscrasia; EM, electron microscopy; NA, not available.

Markowitz, et al. JASN 2001; 12: 1164-1172

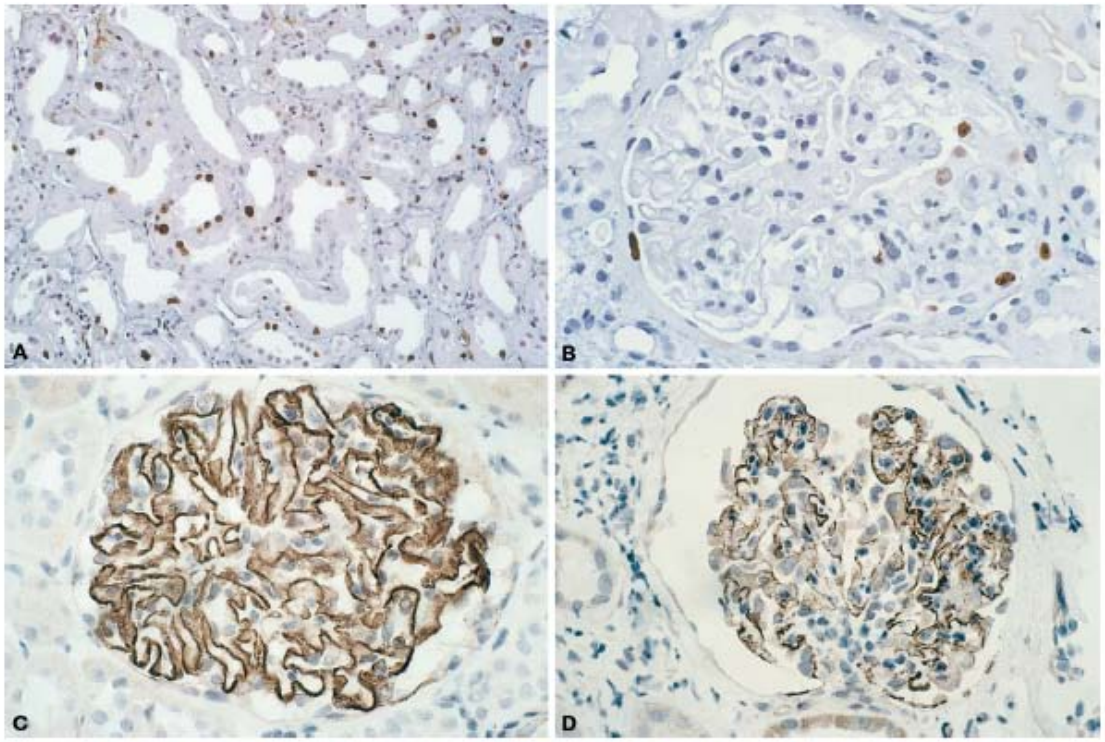


Figure 2. (A) Immunohistochemical staining for proliferation marker Ki-67, showing numerous cell cycle-engaged tubular epithelial cells (patient 2). (B) Immunohistochemical staining for Ki-67 in a glomerulus from patient 7, showing numerous cycling podocytes overlying an area of collapse and a rare positive parietal epithelial cell. (C) Glomerulus from a normal adult control subject, showing intense global immunoreactivity for synaptopodin at the base of the podocytes. (D) Representative glomerulus from patient 2, showing global reduction and segmental loss of podocyte staining for synaptopodin. Magnifications: ×200 in A; ×500 in B; ×400 in C and D.

- Immunohistochemical staining for Ki-67, a proliferation marker, was + in many tubular epithelial cells and scattered visceral epithelial cells in 3 of 4 of the cases studied
- Synaptopodin expression was reduced in the four study cases, with the most extensive loss of expression in the glomeruli with collapsing lesions

Markowitz, et al. JASN 2001; 12: 1164-1172

In summary…

- Temporally, the development of proteinuria and renal insufficiency closely paralleled the administration of pamidronate in escalating doses that exceeded the recommended levels
- There is a combined tubular epithelial and podocyte toxicity from the drug
- The potential mechanism of tubular epithelial toxicity may involve similar mechanisms as those documented in osteoclasts
- Direct podocyte injury is demonstrated by loss of maturity markers

Table 2 | Renal biopsy findings in bisphosphonate-associated nephrotic syndrome

Author/ reference	Patient no.	Clinical presentation	Bisphosphonate	Renal biopsy findings	Bisphosphonate withdrawal?	Outcome following bisphosphonate withdrawal
Markowitz[33]	1	NS/RI	Pamidronate	Collapsing FSGS	No	HD
	2	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
	3	NS/RI	Pamidronate	Collapsing FSGS	No	HD
	4	NS/RI	Pamidronate	Collapsing FSGS	Yes	Increase in sCr
	5	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in sCr
	6	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
	7	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in sCr
Barri[34]	1	NS	Pamidronate	MCD	Yes	Remission of NS
	2	NS	Pamidronate	FSGS NOS	Yes	Persistent NS
	3	NRP/RI	Pamidronate	MCD	Yes	Remission of NRP; decline in sCr
	4	Proteinuria	Pamidronate	FSGS NOS	Yes	Decline in proteinuria; increase in sCr
	5	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
Desikan[35]	1	NRP	Pamidronate	FSGS	Yes	Remission of proteinuria
	2	NRP	Pamidronate	FSGS	Yes	Persistent NRP
Shreedhara[36]	1	NS/RI	Pamidronate	Collapsing FSGS	Yes	Remission of NS & RI
	2	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria & sCr
	3	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria & sCr
Markowitz[37]	1	NS	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria
Lockridge[38]	1	NS/RI	Pamidronate	MCD	Yes	HD
Kunin[39]	1	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
Nasr[40]	1	NS/RI	Pamidronate	Collapsing FSGS & MCN	Yes	Decline in proteinuria & sCr
Bodmer[41]	1	NS/RI	Zoledronate	Collapsing FSGS	Yes	HD

FSGS NOS, FSGS not otherwise specified; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; MCD, minimal change disease; MCN, myeloma cast nephropathy; NRP, nephrotic range proteinuria; NS, nephrotic syndrome; RI, renal insufficiency; sCr, serum creatinine.

- Pamidronate-associated nephrotic syndrome mainly occurs in pts with MM and have received Pamidronate at higher than recommended doses
- The most frequent pathologic lesion is collapsing FSGS, although minimal change and non-collapsing FSGS also seen
- In many cases, the nephrotic syndrome associated with Pamidronate is at least partially reversible

Perazella, et al. Kidney International 2008; 74: 1385-1393.

Zolendronate and ATN

- Case series of 6 patients who developed ATN while on ZA
- 5 patients with MM, one with Pagets
- All received recommended dose of 4mg IV q month
- Mean Cr 1.4 mg/dl prior to treatment, with mean peak Cr 3.5 mg/dl
- All patients underwent renal biopsy

Table 1. Clinical parameters in patients with zoledronate-associated acute tubular necrosis (ATN)

Case number	1	2	3	4	5	6
Age	59	73	57	75	85	66
Gender	Male	Female	Female	Male	Male	Male
Race	C	C	C	C	H	C
Indication for bisphosphonate therapy	MM	Paget's disease	MM	MM	MM	MM
Oncologic treatment						
Total body irradiation	No	No	Yes	No	No	No
Stem cell transplant	Yes	No	Yes	No	No	No
Cisplatin	Single dose	No	No	No	No	No
Pamidronate	Yes	Yes	Yes	Yes	Yes	Yes
Duration of therapy *months*	11	21	46	22	2	8
Maximal dosage *mg/month*	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg
Zoledronate acid						
Duration of therapy *months*	4	4	9	4	3	4
Dose *mg/month*	4	4	4	4	4	4
Infusion time *minutes*	20	15	20	20	15	15
Serum creatinine baseline[a] *mg/dL*	1.9	1.4	1.3	1.4	1.6	1
Renal status at biopsy						
Serum creatinine *mg/dL*	4	3.8	2.5	2.6[b]	5.5	2
24-hour urine protein *g/day*	1.08	2	1.3	Negative	1.7	2.6
Length of post-biopsy follow-up *months*	4	3	4	3	4	1
Final serum creatinine *mg/dL*	2.4	2.6	2.3	1.6	3	1.7
Zoledronate acid discontinued?	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations are: C, Caucasian; H, Hispanic; MM, multiple myeloma.
[a]Prior to zoledronate administration
[b]Case #4 had a serum creatinine of 1.7 mg/dL after treatment with zoledronate, 2.6 mg/dL 2 months later, and 1.6 mg/dL 5 months posttreatment (at the time of biopsy)

Markowitz, et al. KI 2003;64: 281-289

Table 2. Pathologic findings in patients with zoledronate-associated acute tubular necrosis (ATN)

Case number	1	2	3	4	5	6
No. of glomeruli	14	22	40	7	58	19
No. with global GS	1	1	19	2	14	4
No. with focal segmental GS	0	0	0	0	0	0
Tubular degeneration	Diffuse	Diffuse	Diffuse	Diffuse (mild)	Diffuse	Diffuse
TA and IF	Mild	Moderate	Mild	Moderate	Moderate	Mild
Interstitial inflammation	Mild	Moderate	Mild	Mild	Mild	Mild
Vascular disease	Severe	Moderate	Mild	Moderate	Moderate	Severe
PCD-associated disease	No	No	No	No	Yes—MCN & LCDD	No
Immunofluorescence	Negative	Negative	Negative	Negative	Lambda 3+	Negative
EM deposits	No	No	No	No	GBM, MES, TBM	No
EM foot process fusion	25%	20%	NA	10%	15%	50%
Diagnosis—Final	1. ATN 2. HTN	ATN	ATN	ATN	1. ATN 2. MCN 3. LCDD, mild	1. ATN 2. NDGS

Abbreviations are: GS, glomerulosclerosis; TA and IF, tubular atrophy and inerstitial fibrosis; PCD, plasma cell dyscrasia; EM, electron microscopy; MCN, myeloma cast nephropathy; LCDD, light chain deposition disease; GBM, glomerular basement membrane; MES, mesangial; TBM, tubular basement membrane; HTN, hypertensive arterionephrosclerosis; NA, not available; NDGS, nodular diabetic glomerulosclerosis.

- Patient #6 had rare, atypical casts +lambda; given tubular injury out of proportion to casts, and improvement after cessation of ZA without tx of MM, still thought to be ATN 2/2 ZA
- ZA discontinued in 5 patients after renal bx, and in one before (pt #4 discontinued ZA five months prior – had milder tubular injury)

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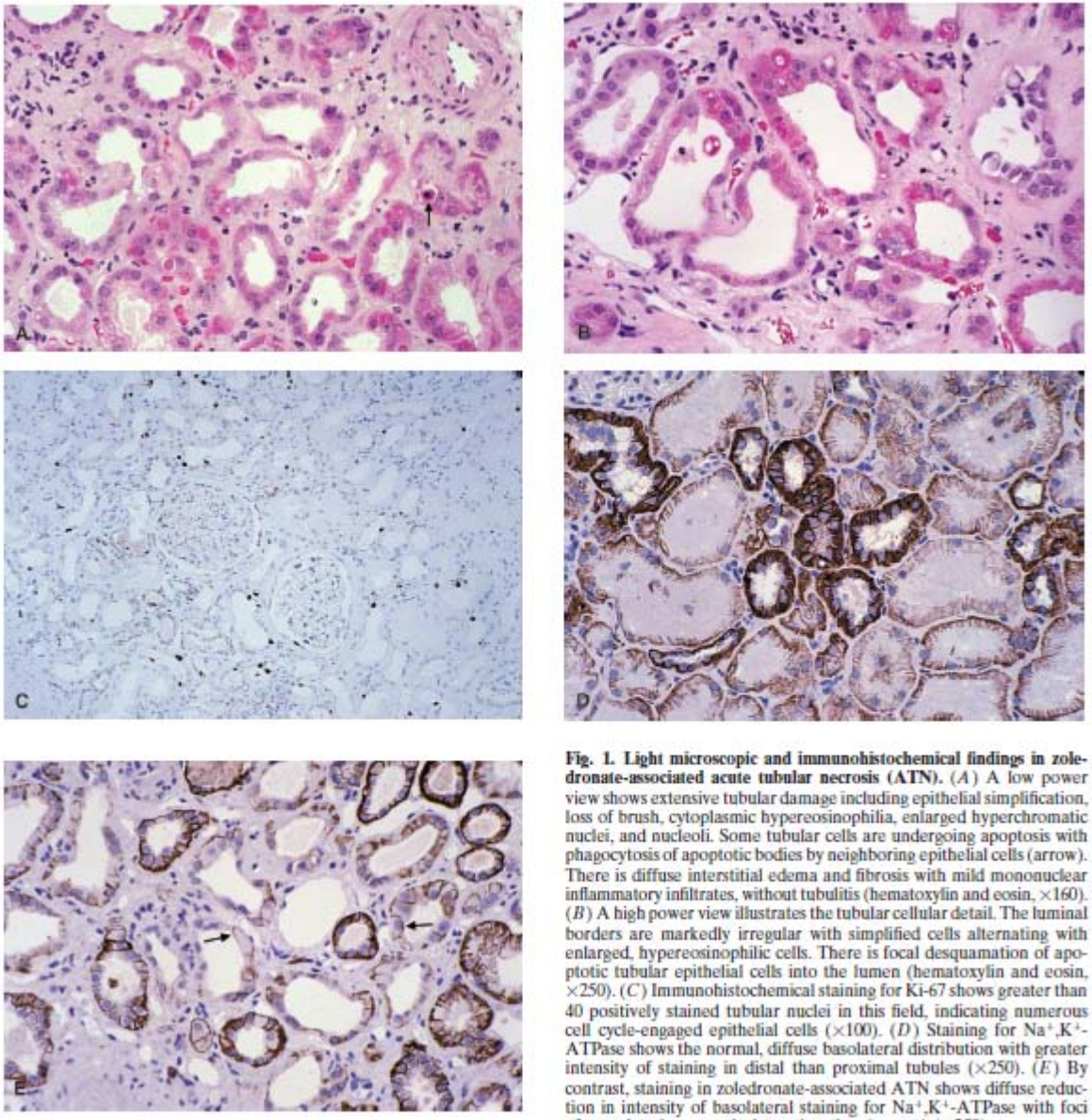


Fig. 1. Light microscopic and immunohistochemical findings in zoledronate-associated acute tubular necrosis (ATN). (*A*) A low power view shows extensive tubular damage including epithelial simplification, loss of brush, cytoplasmic hypereosinophilia, enlarged hyperchromatic nuclei, and nucleoli. Some tubular cells are undergoing apoptosis with phagocytosis of apoptotic bodies by neighboring epithelial cells (arrow). There is diffuse interstitial edema and fibrosis with mild mononuclear inflammatory infiltrates, without tubulitis (hematoxylin and eosin, ×160). (*B*) A high power view illustrates the tubular cellular detail. The luminal borders are markedly irregular with simplified cells alternating with enlarged, hypereosinophilic cells. There is focal desquamation of apoptotic tubular epithelial cells into the lumen (hematoxylin and eosin, ×250). (*C*) Immunohistochemical staining for Ki-67 shows greater than 40 positively stained tubular nuclei in this field, indicating numerous cell cycle-engaged epithelial cells (×100). (*D*) Staining for Na^+,K^+-ATPase shows the normal, diffuse basolateral distribution with greater intensity of staining in distal than proximal tubules (×250). (*E*) By contrast, staining in zoledronate-associated ATN shows diffuse reduction in intensity of basolateral staining for Na^+,K^+-ATPase with foci of complete loss or apical translocation (arrows) (×250).

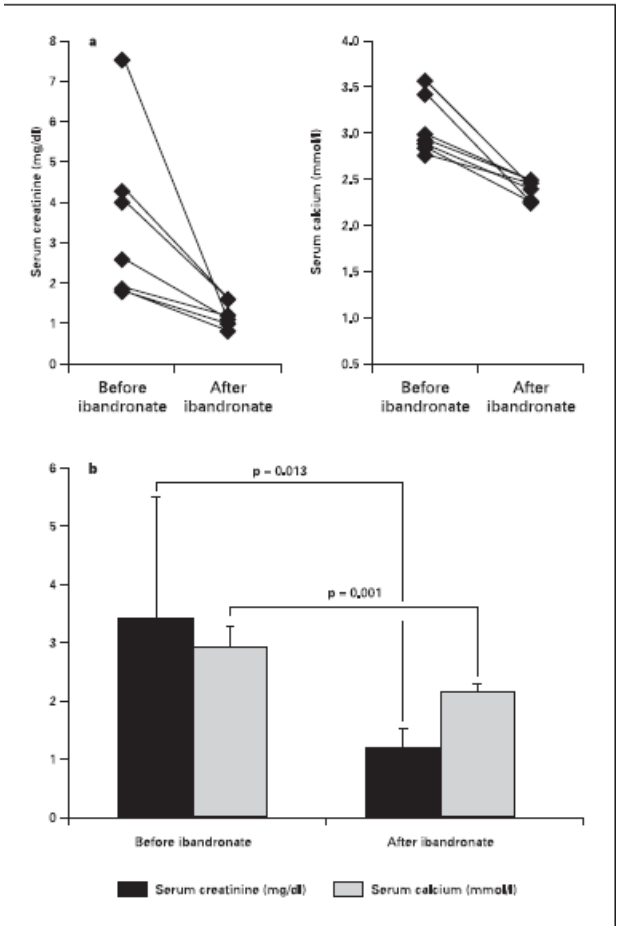
Markowitz, et al. KI 2003;64: 281-289

Conclusions of the study

- The renal biopsy findings of diffuse tubular injury in the absence of glomerular abnormalities or significant interstitial inflammation, tubulitis, or eosinophils suggest that zoledronate acts as an epithelial toxin that targets proximal tubules.
- This is supported by the immunohistochemical findings with high-dose pamidronate has been associated with of a marked increase in cell-cycle engaged (Ki-67 positive) tubular epithelial cells and the marked derangement in tubular Na,K-ATPase expression
- Proposed mechanism is that ZA is taken up by proximal tubule cells the same way it is by osteoclasts, and similarly impair cell energetics by inhibiting the mevalonate pathway
- Given temporal association with ZA and known potential for renal toxicity based on prior large studies, ZA believed to be the etiology
- All pts experienced improvement in renal function after discontinuation of the ZA

Ibandronate

- Small case series looking at the safety and efficacy of using Ibandronate in patients with renal insufficiency
- 7 patients with MM, with acute renal failure (CrCl 9-37) and hypercalcemia (Ca 2.59-3.63 mmol/L)
- 4 patients had renal biopsies: 1 revealing cast nephropathy and 3 with nephrocalcinosis
- Ibandronate 2-6mg IV was infused over 30min



- Serum calcium levels were effectively lowered to the normal range in all 7 patients; Renal function improved in all patients
- Higher degree of protein binding is thought to be renally-protective: reduces risk of rapid influx to renal tubule cells
- Shorter renal tissue half-life, possibly allowing more time for injured cells to undergo repair in between dosing

Summary of Bisphosphonate Nephrotoxicity

- Large, placebo-controlled studies looking at the efficacy of bisphosphonates at reducing skeletal complications and bone pain have reported cases of worsening renal function, without providing data on renal histological evaluation
- Smaller case series:
  - Pamindronate: Collapsing FSGS
  - Zolendronate: Acute tubular necrosis
- Ibandronate: safer renal profile
  - Argues against a class effect
  - Not yet FDA-approved for this indication in the United States
  - Longer term and larger studies are needed to assess its efficacy and safety

Current recommendations

Table 1 | Bisphosphonate dosing for malignancy-associated hypercalcemia or osteolytic disease

Drug	Dose/infusion time	Interval
	Estimated CrCl >60 cc/min	
Pamidronate	90 mg over 2–3 h	3–4 weeks
Zoledronate	4 mg over 15 min	3–4 weeks
	Estimated CrCl 30 <60 cc/min	
Pamidronate	90 mg over 2–3 h[a]	3–4 weeks
Zoledronate	Reduced dosage[b]	3–4 weeks
	Estimated CrCl <30 cc/min	
Pamidronate	90 mg over 4–6 h[a]	3–4 weeks
Zoledronate	Not recommended	

CrCl, creatinine clearance.
[a]Consider dose reduction (ASCO 2007; Kyle *et al.*[4]).
[b]3.5 mg (CrCl, 50–60 cc/min); 3.3 mg (CrCl, 40–49 cc/min); 3 mg (CrCl, 30–39 cc/min); Reference http://www.pharma.us.novartis.com/product/pi/pdf/Zometa.pdf.

Thank you